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Effects of Replacement Dose of Dehydroepiandrosterone in Men and Women of Advancing Age*

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ABSTRACT

Aging in humans is accompanied by a progressive decline in the secretion of the adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulfate (DS), paralleling that of the GH-insulin-like growth factor-I (GH-IGF-I) axis. Although the functional relationship of the decline of the GH-IGF-I system and catabolism is recognized, the biological role of DHEA in human aging remains undefined. To test the hypothesis that the decline in DHEA may contribute to the shift from anabolism to catabolism associated with aging, we studied the effect of a replacement dose of DHEA in 13 men and 17 women, 40–70 yr of age. A randomized placebo-controlled cross-over trial of nightly oral DHEA administration (50 mg) of 6-month duration was conducted. During each treatment period, concentrations of androgens, lipids, apolipoproteins, IGF-I, IGF-binding protein-1 (IGFBP-1), IGFBP-3, insulin sensitivity, percent body fat, libido, and sense of well-being were measured. A subgroup of men ($n = 8$) and women ($n = 6$) underwent 24-h sampling at 20-min intervals for GH determinations.

DHEA and DS serum levels were restored to those found in young adults within 2 weeks of DHEA replacement and were sustained throughout the 3 months of the study. A 2-fold increase in serum levels

of androgens (androstenedione, testosterone, and dihydrotestosterone) was observed in women, with only a small rise in androstenedione in men. There was no change in circulating levels of sex hormone-binding globulin, estrone, or estradiol in either gender. High density lipoprotein levels declined slightly in women, with no other lipid changes noted for either gender. Insulin sensitivity and percent body fat were unaltered. Although mean 24-h GH and IGFBP-3 levels were unchanged, serum IGF-I levels increased significantly, and IGFBP-1 decreased significantly for both genders, suggesting an increased bioavailability of IGF-I to target tissues. This was associated with a remarkable increase in perceived physical and psychological well-being for both men (87%) and women (84%) and no change in libido.

In conclusion, restoring DHEA and DS to young adult levels in men and women of advancing age induced an increase in the bioavailability of IGF-I, as reflected by an increase in IGF-I and a decrease in IGFBP-1 levels. These observations together with improvement of physical and psychological well-being in both genders and the absence of side-effects constitute the first demonstration of novel effects of DHEA replacement in age-advanced men and women. (*J Clin Endocrinol Metab* 78: 1360–1367, 1994)

AGING in man is associated with reduced protein synthesis, decreased lean body mass and bone mass, and increased body fat (1). These body composition changes are accompanied by a progressive decline of adrenal secretion of dehydroepiandrosterone (DHEA) and its sulfate ester (DS) (2) paralleling that of the GH-insulin-like growth factor-I (GH-IGF-I) system (1). Although the GH-IGF-I system is recognized as a trophic factor in promoting cellular growth and metabolism at multiple sites (1, 3), the biological role of DHEA and DS in humans remains elusive. Based on animal experiments, DHEA may be viewed as a multifunctional steroid with protective roles in many aspects of cellular well-being, especially aging-associated deficits (4–7). The rele-

vance of these findings to human biology and diseases is perplexing, because adrenal production of DHEA or DS in these experimental animals is either minute or does not exist; humans and nonhuman primates are the only species with the capacity to synthesize and secrete these adrenal androgens in quantities surpassing all other known steroids (8–10).

Epidemiological data support beneficial effects of DHEA and DS. Low serum DS levels are correlated with increased cardiovascular morbidity in men (11), breast cancer in women (12), and the decline of immunocompetence during aging (13). However, prospective studies (14, 15) failed to confirm earlier reports of an inverse association of plasma DS levels and angiographically defined coronary atherosclerosis in men (16) and a positive correlation of serum DS levels and bone mineral density in aging women (17).

In healthy young men, using suprapharmacological doses of DHEA (1600 mg/day) for 4 weeks, Nestler *et al.* (18) reported a decrease in cholesterol and low density lipoprotein (LDL) levels as well as a 31% decrease in body fat without weight changes, implying an increase in muscle mass (18); these findings, however, were not confirmed by subsequent reports using the same dose of DHEA in obese (19) and nonobese (20) young men and in postmenopausal women (21). All clinical studies thus far were conducted with mega-

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‡ Clayton Foundation investigator.

doses of DHEA, which may induce responses beyond its physiological action or even induce down-regulation of cellular response.

In the present study, we tested the supposition that restoring extracellular levels of DHEA and DS in individuals of advancing age to levels in young adults may have beneficial effects on neuroendocrine-metabolic functions. We report here the results of a replacement dose of 50 mg DHEA administered orally at bedtime to 17 women and 13 men, aged 40–70 yr, in a double blind, placebo cross-over trial of 6-month duration.

Materials and Methods

Subjects

Subjects were recruited by advertisement. 17 women (mean, 54.5 \pm 1.9 yr) and 13 men (mean, 53.7 \pm 2.5 yr), aged 40–70 yr, were entered into the study. There were 5 subjects of each gender in each decade of the age group, except for only 3 men in the fourth decade and 6 women each in the fifth and sixth decades. All subjects were nonobese with a body mass index (BMI) of 20–28 kg/m² (mean, 24.5 \pm 0.6 kg/m² for women, 26.6 \pm 0.7 kg/m² for men) and were nonsmokers; they were taking no medications and had stable dietary and exercise regimens. Of the 17 women, 2 were premenopausal, and 15 were menopausal. Of these 15, 8 were receiving menopausal estrogen replacement (previous hysterectomy), whereas the other 7 women were receiving no menopausal replacement therapy. Medical illness was excluded by history, physical examination, blood chemistry profile (including renal, hepatic, and thyroid panels), urinalysis, and complete blood count. All subjects completed the protocol. The protocol was approved by the Committee on Investigations Involving Human Subjects of the University of California-San Diego. All subjects gave oral and written informed consent.

Study design

The study design was a randomized, double blind, placebo cross-over trial of 6-month duration. Sample size in this trial was calculated using a computer software package (Power and Sample Size by J. L. Hintze) by estimating the α error at 0.05, the β error at 0.25 (power 75%), and Δ (size of treatment effect sought) of 1 sd of the measurement of the outcome variable.

The daily replacement oral dose of 50 mg DHEA was determined by taking into account the MCR of 11–15 L/day, a daily production rate of 18–28 mg for DS, interconversion rates of DHEA to DS of 7.7% and DS to DHEA of 30% (22, 23), estimated endogenous serum levels in individuals of advancing age of 20–40% young adult levels (2, 24), and absorption of 50% of an oral dose (21).

Each subject received 3 months of DHEA and 3 months of placebo at bedtime in random order. Compliance was checked by pill counts and monthly refills and retrospectively by DHEA and DS levels. All subjects were instructed by a nutritionist to continue their current and usual dietary and exercise regimens. A questionnaire was administered at monthly intervals for dietary recall, using household measures (25). These records were coded and analyzed using the Nutrition III version 7 software program. No major changes in the diet/exercise regimen of individuals occurred over the duration of the trial.

Study protocol and procedures

Potential adverse effects were monitored by means of interviews, physical examinations, and standard laboratory tests. Subjects were seen monthly as well as 2 weeks after their baseline and 3 and 6 month visits. Blood was drawn at each visit between 0800–0900 h after an overnight fast for determination of serum steroid hormones and sex hormone-binding globulin (SHBG) levels as well as liver function, renal function, electrolytes, complete blood count, and urinalysis.

At the baseline, 3 month, and 6 month visits, an additional fasting

blood sample was collected for lipids, IGF-I, IGF-binding protein-1 (IGFBP-1), IGFBP-3, insulin, and glucose determinations. During each of these visits, the heights and weights of all subjects were recorded as well as an estimation of percent body fat by bioelectric impedance (B-101A RJL System, Detroit, MI) (26–28). Insulin sensitivity was assessed in all subjects by the modified, minimally sampled, iv glucose tolerance test (29): administration of 300 mg/kg dextrose as an iv bolus over 1 min, followed 20 min later by an iv bolus of regular insulin (0.03 U/kg). Frequent blood samples were obtained (at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 min) for determinations of serum glucose and insulin. Insulin sensitivity and glucose effectiveness were analyzed using the MINMOD computer program (30). In a subgroup of five subjects, insulin sensitivity was further measured using the hyperinsulinemic euglycemic clamp method at baseline and 3 and 6 months. A visual analog scale of libido and an open ended questionnaire for self-assessment of well-being and activities as well as side-effects were administered at the 3 (cross-over) and 6 month visits.

A subgroup of 13 of the 30 subjects (8 men and 5 women) was admitted to the Clinical Research Center for 24-h frequent blood sampling (every 20 minutes) from 0800–0800 h for determination of serum GH profiles at baseline and 3 and 6 months. Meals were served at 0800, 1200, and 1700 h, and subjects slept from 2200–0700 h.

Another subgroup of five subjects (three men and two women) was admitted to the Clinical Research Center for hyperinsulinemic euglycemic clamp studies, according to previously described procedures (31), to assess tissue sensitivity to insulin, expressed as the glucose disposal rate (milligrams per kg/min) at baseline and 3 and 6 months. Briefly, a catheter was inserted into an antecubital vein for infusion of insulin and glucose. A second catheter was inserted retrogradely into a dorsal hand vein, which was kept in a heating device, for sampling of arterialized venous blood. Recombinant human regular insulin was infused via a Harvard pump at a rate of 40 mU/m²·min for a total of 240 min. Serum glucose was maintained at 4.7–5.3 mmol/L by adjustments of a variable infusion of 20% glucose based on the glucose values determined at 5-min intervals. Whole body glucose disposal rates were calculated by determining the mean of data from the last 60 min of the study on each occasion, corrected for residual hepatic glucose output measured by isotope dilution (32).

Assays

All hormone measurements for an individual subject were performed in the same assay. Serum concentrations of DHEA, DS, testosterone (T), androstenedione (A'dione), estrone (E₁), estradiol (E₂), and dihydrotestosterone (DHT) were measured by specific RIAs, previously described (33). The sensitivity of the assays were 0.3 nmol/L for DHEA, 0.6 μ mol/L for DS, 0.3 nmol/L for T, 0.6 nmol/L for A'dione, 42 pmol/L for E₁, 44 pmol/L for E₂, and 0.2 nmol/L for DHT. The intra- and interassay coefficients of variation were, respectively, 8% and 9% for DHEA, 5% and 7% for DS, 5% and 6% for T, 4% and 11% for A'dione, 11% and 12% for E₁, 9% and 10% for E₂, and 8% and 11% for DHT.

Serum GH levels were measured by an established RIA (34) with a sensitivity of 0.5 μ g/L and intra- and interassay coefficients of 5% and 9%, respectively. IGF-I, IGFBP-1, and IGFBP-3 were determined by established RIAs at Nichols Institute Reference Laboratories (San Juan Capistrano, CA). IGF-I was measured after acid-ethanol extraction (35, 36) with an assay sensitivity of 0.1 ng/mL and intra- and interassay coefficients of variation of 5.0% and 10.2%, respectively. RIAs for IGFBP-1 and IGFBP-3 have sensitivities, respectively, of 1 ng/mL and 0.1 mg/L and intra- and interassay coefficients of variation, respectively, of less than 5% and 14.2% for IGFBP-1 and 3% and 7.2% for IGFBP-3 (37, 38).

SHBG was measured by time-resolved fluoroimmunoassay (Delfia SHBG kit, Wallac, Gaithersburg, MD), with a sensitivity of 0.8 nmol/L and intra- and interassay coefficients of variation, respectively, of 7% and 9%. Serum glucose concentrations were determined by the glucose oxidase method (Yellow Springs Instrument Co. analyzer, Yellow Springs, OH). Serum insulin levels were measured by a double antibody RIA, with an assay sensitivity of 2.1 μ U/mL, and intra- and interassay coefficients of variation of 7% and 9%, respectively (39).

Serum total cholesterol and triglycerides were measured by previously described enzymatic methods (40, 41). Very low density lipoprotein was

calculated by dividing the triglyceride value by 5. LDL cholesterol was calculated using the formula: $LDL = \text{cholesterol} - (\text{HDL} + \text{very low density lipoprotein})$. HDL cholesterol was enzymatically determined after sodium phosphotungstate/magnesium precipitation of other lipids. Apolipoprotein-A-1 and -B were quantified by Behring nephelometry. Coefficients of variations vary from 2–10%. Complete blood counts, liver function studies, thyroid panel, electrolytes, and urinalysis, used to monitor subject safety, were performed in a commercial laboratory (MetWest Unilabs, San Diego, CA).

Analyses of data

GH pulsatile activity was analyzed using the Cluster pulse detection algorithm, with a cluster configuration of 2×2 and t statistics of 2.5×2.5 (42). Differences between all steroid hormone concentrations as well as SHBG at the monthly time points were performed by two-way analysis of variance with repeated measures, with factors gender and treatment, followed by Dunnett's testing. Lipids, BMI, percent body fat, insulin sensitivity, glucose effectiveness, glucose disposal rates, GH parameters, IGF-I, IGFBP-1, and IGFBP-3 were analyzed by an analogous two-way analysis of variance, followed by *post-hoc* Dunnett's testing for comparing treatment groups (DHEA and placebo) to baseline (control). Differences in self-reported well-being and libido were analyzed by paired t tests (two tailed). Data are presented as the mean (\pm SE), and $P < 0.05$ was considered significant for all analyses.

Results

Steroid hormone changes

In response to DHEA administration, within 2 weeks, serum levels of DHEA and DS were elevated from placebo values in both men (8.47 ± 0.8 to 14.72 ± 1.4 nmol/L; 3.5 ± 0.3 to 10.1 ± 1.2 μ mol/L; $P < 0.001$) and women (7.19 ± 0.5 to 16.13 ± 1.3 nmol/L; 1.78 ± 0.17 to 9.27 ± 0.76 μ mol/L; $P < 0.001$) respectively (Fig. 1). The incremental levels attained were in the range of young adult levels (2). These levels were maintained throughout the 3-month trial based on monthly determinations and were normalized within 2 weeks after discontinuation of DHEA (data not shown). Serum levels of DS attained with DHEA treatment were not significantly correlated to baseline DS levels for men ($r = 0.21$; $P = 0.5$) or women ($r = -0.22$; $P = 0.4$).

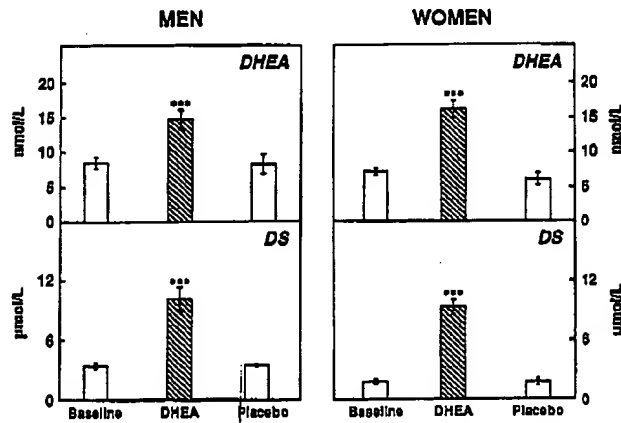


FIG. 1. Mean (\pm SE) serum DHEA and DS concentrations in men (left panel) and women at baseline, after 12 weeks of oral administration of 50 mg DHEA nightly, and after 12 weeks of placebo administration. ***, $P < 0.005$ compared with placebo values.

Biotransformation of DHEA to potent androgens occurred selectively in women (Fig. 2, right panel). Between baseline and 12 weeks of DHEA administration in women, serum A'dione increased from 1.33 ± 0.13 to 3.0 ± 0.19 nmol/L ($P < 0.001$), serum T from 0.72 ± 0.07 to 1.46 ± 0.14 nmol/L ($P < 0.001$), and serum DHT from 0.32 ± 0.03 to 0.9 ± 0.1 nmol/L ($P < 0.001$), whereas serum SHBG concentrations exhibited a tendency to decline (105.5 ± 12.3 to 81.2 ± 10.6 nmol/L) that was not statistically significant. In men, there was no significant change in serum T, DHT, or SHBG concentrations with baseline, DHEA, or placebo administration. Serum A'dione levels, however, increased significantly during DHEA treatment (1.86 ± 0.11 to 2.23 ± 0.14 nmol/L; $P < 0.01$; Fig. 2, left panel). Serum levels of E_1 and E_2 were not significantly altered, in men (E_1 , 89.4 ± 5.9 vs. 95.0 ± 7.8 pmol/L; E_2 , 87.7 ± 4.8 vs. 78.3 ± 6.6 pmol/L), and women (E_1 , 256.2 ± 58.5 vs. 268.2 ± 58.8 pmol/L; E_2 , 144.7 ± 35.2 vs. 107.3 ± 20.6 pmol/L).

Lipids (Table 1)

Serum lipids, triglycerides, and apolipoprotein-B and -A-1 did not change in men and women, with the exception of serum HDL in women, which was reduced during DHEA

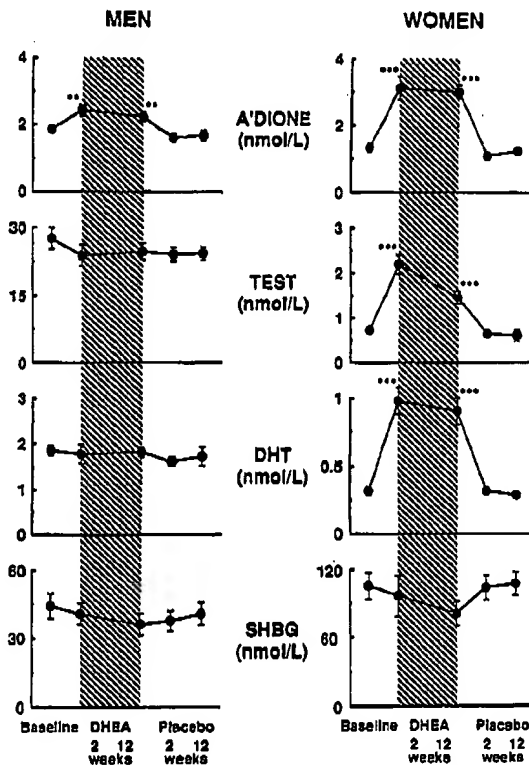


FIG. 2. Serum concentrations of androgens and SHBG in men (left panel) and women at baseline, 2 and 12 weeks after oral administration of 50 mg DHEA nightly, and 2 and 12 weeks after placebo administration. The shaded area represents the DHEA treatment period. **, $P < 0.01$; ***, $P < 0.005$ (compared with basal values). TEST, T.

DHEA REPLACEMENT

1363

TABLE 1. Effects of replacement dose of DHEA and placebo on cholesterol and lipoprotein levels in men ($n = 13$) and women ($n = 17$)

	Men	Women
Cholesterol (mg/dL)		
Placebo	204.3 \pm 7.9	223.7 \pm 5.8
DHEA	209.9 \pm 9.4	218.3 \pm 6.9
HDL (mg/dL)		
Placebo	45.4 \pm 2.5	68.7 \pm 2.6
DHEA	44.8 \pm 1.7	68.4 \pm 2.7*
LDL (mg/dL)		
Placebo	140.4 \pm 6.9	141.2 \pm 6.2
DHEA	147.5 \pm 8.5	136.0 \pm 4.9
Apo-A1 (mg/dL)		
Placebo	165.4 \pm 5.3	222.8 \pm 8.1
DHEA	167.4 \pm 6.1	213.7 \pm 8.1
Apo-B (mg/dL)		
Placebo	148.0 \pm 7.3	137.2 \pm 5.8
DHEA	149.8 \pm 8.5	137.4 \pm 5.9
TG		
Placebo	114.5 \pm 18.5	102.5 \pm 9.2
DHEA	107.7 \pm 10.5	94.2 \pm 7.4

HDL, High density lipoprotein; Apo-A1, apolipoprotein-A1; Apo-B, apolipoprotein-B; TG, triglycerides. Values are the mean \pm SEM.

* $P < 0.05$ compared to placebo.

treatment (68.7 \pm 2.6 to 63.4 \pm 2.7 mg/dL; $P < 0.05$) compared with placebo.

Anthropometric measures and glucose metabolism (Table 2)

There was no significant change in anthropometric indices (percent body fat or BMI) during either DHEA or placebo treatment in men or women.

Insulin sensitivity and the insulin-independent fractional glucose disappearance, glucose effectiveness, as determined by Bergman's modified minimal model technique, did not change significantly during DHEA administration in either men or women. Similarly, glucose disposal rates as determined by the hyperinsulinemic euglycemic clamp in three men and two women showed no significant difference with DHEA or placebo administration (DHEA, 7.64 \pm 0.56 mg/kg·min; placebo, 8.41 \pm 1.26 mg/kg·min).

Well-being and libido

An improved sense of well-being was self-reported by the majority of women (82%) as well as men (67%) after 12 weeks of DHEA administration, whereas less than 10% reported any change after placebo administration (Fig. 3, left panel). Specific statements of well-being ranged from improved quality of sleep, more relaxed, increased energy to

better ability to handle stress. No difference was noted in libido while subjects were receiving DHEA compared to the placebo group (Fig. 3, right panel). Of note, there were five subjects who self-reported marked improvements of preexisting joint pains and mobility during DHEA replacement.

GH-IGF axis

There was no difference noted in GH pulse number per 24 h, mean amplitude, or transverse mean in the subset of 13 subjects (8 men and 5 women) who underwent 24-h frequent blood sampling for GH (Table 3). A representative example of 24-h GH pulsatile activity at baseline and in response to the administration of DHEA vs. placebo is displayed in Fig. 4.

In response to DHEA administration, men (Fig. 5, left panel) showed an elevation of serum IGF-I levels (151.3 \pm 10.2 to 180.1 \pm 15.4 ng/mL; $P < 0.01$) and a decline in IGFBP-1 levels (28.7 \pm 3.3 to 20.4 \pm 3.5 ng/mL; $P < 0.05$), resulting in an increased IGF-I/IGFBP-1 ratio (8.3 \pm 1.6 to 12.7 \pm 2.9; $P < 0.05$). A similar finding was seen in women (Fig. 5, right panel), with elevation of serum IGF-I levels (140.8 \pm 14.0 to 157.4 \pm 16.4 ng/mL; $P < 0.05$) and a decline in IGFBP-1 levels (53.2 \pm 6.6 to 41.3 \pm 5.7 ng/mL; $P < 0.01$), resulting in an increased IGF-I/IGFBP-1 ratio (4.2 \pm 1.1 to 6.6 \pm 1.9; $P < 0.05$). There was no change in IGFBP-3 levels in men (2.8 \pm 0.2 to 2.6 \pm 0.2 ng/mL) or women (2.8 \pm 0.1 to 2.8 \pm 0.1 mg/L; Fig. 5).

Although the baseline IGF-I levels were similar, a significant gender difference was noted in baseline IGFBP-1 levels, with women having a 2-fold higher level than men (women, 51.0 \pm 7.0; men, 25.5 \pm 4.1; $P < 0.01$), which confirms the report of Yeoh and Baxter (43). Consequently, a significantly lower IGF-I/IGFBP-1 ratio occurs in women ($P < 0.05$; Fig. 6A). Given this gender difference, the data were further analyzed to determine whether the relative changes from placebo group values for men and women differed. As shown in Fig. 6B, the individual percent change from placebo for IGF-I and IGFBP-1 values in both genders were fairly uniform. An increase in IGF-I in men (11.3 \pm 4.8%; $P < 0.05$) and women (9.7 \pm 5.0%; $P < 0.05$) as well as a significant decrease in IGFBP-1 in men (20.7 \pm 6.7%; $P < 0.05$) and women (18.3 \pm 6.2%; $P < 0.05$) imposed by DHEA administration relative to placebo group values were evident. Consequently, the IGF-I/IGFBP-1 ratio, an index that may reflect an overall increase in the bioavailability of IGF-I, was increased in both men (52.0 \pm 15.9%; $P < 0.05$) and women (54.1 \pm 15.1%; $P < 0.05$) to a similar extent. Whether

TABLE 2. Effects of replacement dose of DHEA and placebo on body composition and glucose metabolism in men ($n = 13$) and women ($n = 17$)

	Men		Women	
	Placebo	DHEA	Placebo	DHEA
% Fat	22.1 \pm 1.2	21.9 \pm 1.8	31.0 \pm 1.0	31.3 \pm 1.0
BMI (kg/m ²)	27.3 \pm 0.8	27.0 \pm 0.7	24.8 \pm 0.7	24.7 \pm 0.7
Insulin sensitivity ($\times 10^{-4}$ min/ μ U·mL)	2.89 \pm 0.6	3.69 \pm 0.5	3.72 \pm 0.5	2.90 \pm 0.4
Glucose effectiveness (min ⁻¹)	0.022 \pm .002	0.019 \pm 0.001	0.018 \pm 0.001	0.024 \pm .002

Values are the mean \pm SEM.

FIG. 3. Percentage of men and women who self-reported an improved sense of well-being after 12 weeks of oral administration of 50 mg DHEA nightly and after 12 weeks of placebo administration (left panel). ***, $P < 0.005$ compared with placebo values. Scored values of libido on a visual analog scale in men and women after 12 weeks of oral administration of 50 mg DHEA nightly and after 12 weeks of placebo administration are shown. **, $P < 0.01$ compared with opposite gender values.

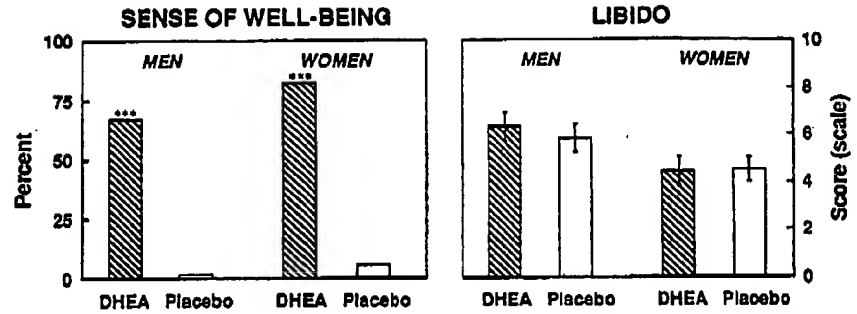


TABLE 3. Effects of replacement dose of DHEA and placebo on 24-h GH characteristics in men ($n = 8$) and women ($n = 5$)

	Pulse no./24 h	Amplitude ($\mu\text{g/L}$)	Transverse mean ($\mu\text{g/L}$)
Baseline	6.00 \pm 0.45	3.65 \pm 0.73	2.19 \pm 0.27
DHEA	5.23 \pm 0.55	2.49 \pm 0.45	2.05 \pm 0.28
Placebo	5.54 \pm 0.60	3.17 \pm 0.76	2.05 \pm 0.27

Values are the mean \pm SEM.

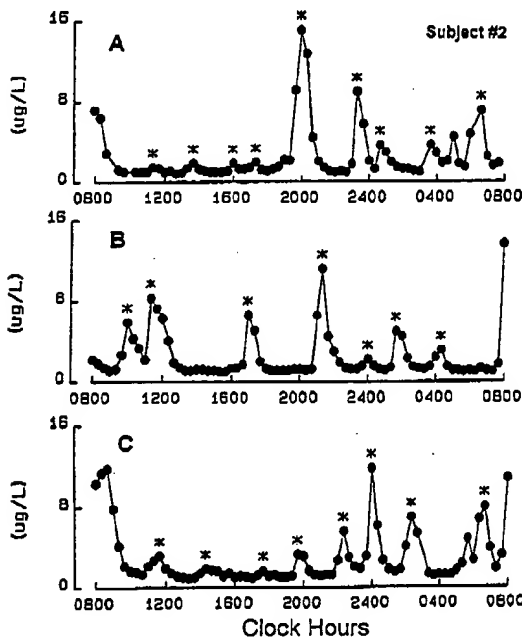


FIG. 4. Twenty-four-hour serum GH pulsatile pattern in a representative subject (a 47-yr-old woman, subject 2) at baseline (A), after 12 weeks of oral administration of 50 mg DHEA nightly (B), and after 12 weeks of placebo (C) administration. *, Identified pulses.

postmenopausal women were with ($n = 8$) or without ($n = 7$) estrogen replacement was not a significant factor in the relative increase in the ratio of IGF-I/IGFBP-1 (with estrogen, 48%; without estrogen, 66%; $P = \text{NS}$). Serum levels of IGF-I and IGFBP-1 attained with DHEA treatment were not significantly correlated to basal levels.

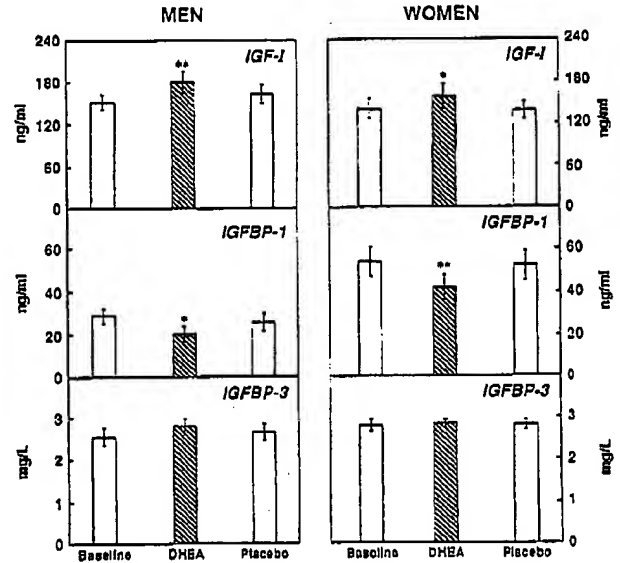


FIG. 5. Serum IGF-I, IGFBP-1, and IGFBP-3 concentrations in men (left panel) and women at baseline, after oral administration of 50 mg DHEA nightly for 12 weeks, and after placebo for 12 weeks. *, $P < 0.05$; **, $P < 0.01$ (compared with placebo values).

Safety studies

Physical examination, hepatic and thyroid studies, complete blood count, and urinalysis revealed no abnormalities or significant changes throughout the study. One female subject reported increased facial hair during DHEA treatment, and one did so during placebo; both resolved by the end of 3 months of the other treatment period.

Discussion

In the present study, we have demonstrated that a calculated replacement dose of 50 mg DHEA administered orally at bedtime to men and women of advancing age restored DHEA and DS to levels seen in the second decade of life (2). These levels were sustained throughout the 3 months of DHEA administration. The use of physiological replacement rather than pharmacological doses of DHEA may be of critical importance in determining the effects of DHEA and DS in the aging population, because of its ability to undergo

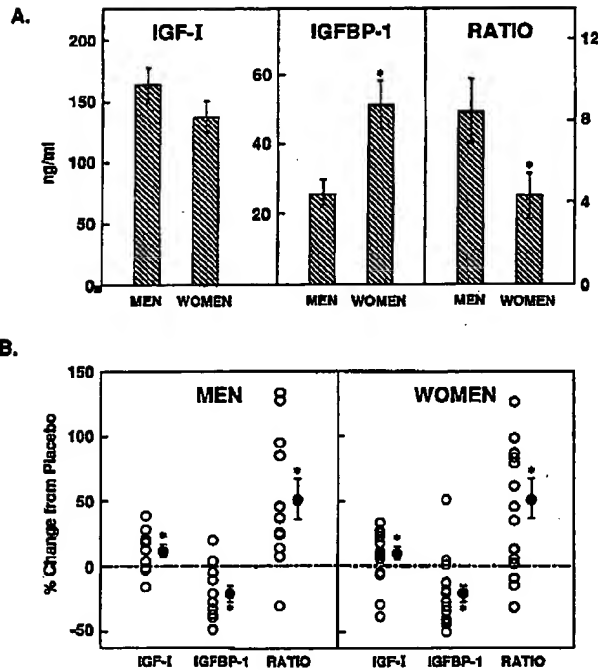


FIG. 6. A, Baseline (mean \pm SE) serum IGF-I and IGFBP-1 concentrations and their ratio (IGF-I/IGFBP-1) in men and women. *, $P < 0.05$; **, $P < 0.01$ (compared with opposite gender value). B, Percent change from placebo of individual values for serum IGF-I, IGFBP-1, and IGF-I/IGFBP-1 ratio after 12 weeks of oral administration of 50 mg DHEA nightly in men and women. The mean \pm SE of each measurement are also shown. *, $P < 0.05$ compared with placebo.

rapid biotransformation to potent androgens, which, in turn, may have a biological impact on target tissue, including anabolic effects. To date, only one study was designed to address the issue of the pharmacological impact of DHEA. Mortola and Yen (21), using a 1600-mg daily oral dose of DHEA in postmenopausal women (aged 46–61 yr) for 4 weeks, demonstrated a marked biotransformation of DHEA to potent androgens and estrogens. The increments reached 9-fold for T, 20-fold for A'dione and DHT, and 2-fold for E_1 and E_2 . This hyperandrogenic state imposed by a pharmacological dose of DHEA was associated with a significant decline in SHBG, T_4 -binding globulin, total cholesterol, and high density lipoprotein cholesterol and the appearance of insulin resistance. These marked endocrine-metabolic changes were not observed in our present study with a replacement dose of DHEA. The increments in androgens, but not estrogens, were minimal and occurred selectively in women. Most importantly, these levels were within the normal ranges of adult women (44). Thus, within our experimental design, the results obtained may reflect the physiological actions of DHEA *in vivo*.

The most intriguing observation made in the present study was changes in the IGF-I system. DHEA replacement induced an approximately 10% rise in serum IGF-I levels and an approximately 19% decline in IGFBP-1 levels, resulting in an elevation of IGF-I/IGFBP-1 ratio by 50% in both men

and women. These changes occurred independent of gender differences in baseline IGFBP-1 levels and were unaccompanied by changes in insulin sensitivity and 24-h GH or GH-dependent IGFBP-3 levels.

IGF-I, a potent metabolic growth factor, is regulated by GH and secreted constitutively by the liver without storage (45). To maintain steady levels in the circulation, IGF-I is bound to a series of IGFBPs. The major BP in serum is IGFBP-3, which possesses the highest binding affinity for IGFs and is completely saturated (46). Serum IGFBP-1 is present with a relatively low binding affinity and at a 100-fold lower concentration than IGFBP-3, but is unsaturated and binds IGFs readily (45–47). That IGFBP-1 may play a physiological role by modulating the availability of IGF-I for metabolic homeostasis is suggested by its ability *in vivo* to block IGF-I action and increase blood glucose levels after the administration of IGFBP-1 (45). IGFBP-1 is mainly expressed in the liver, and its release is suppressed by insulin (45–47) and GH (48). Given this background, the effect of DHEA on IGF-I/IGFBP-1 observed in the present study appears to be operating outside the known regulatory mechanism of the GH-IGF-I and insulin-IGFBP-1 axes. In the absence of a known mechanism of DHEA action, we speculate that restoration of DHEA levels in men and women of advancing age may exert a stimulatory action on either the hepatic production of IGF-I or the generation of GH receptors, thereby enhancing the effectiveness of ambient GH levels for IGF-I production. In the same context, hepatic production of IGFBP-1 may be inhibited by DHEA to account for the increased IGF-I/IGFBP-1 ratio without a discernible change in GH or insulin levels. The possibility that DHEA may represent a previously unrecognized physiological regulator of the IGF-I/IGFBP-1 system should be considered an issue that deserves further investigation.

It is also not known whether this relative increase in the bioavailability of IGF-I in response to DHEA in time may exert a metabolic impact on anabolism or attenuate ongoing catabolism. The role of IGF-I in reversing catabolism has been recognized in experiments of GH administration in aging populations (3). Several IGF-I infusion studies, as recently reviewed by Clemmons (49), have shown that acute elevation of IGF-I levels can induce a glucose-lowering and protein-sparing effect in healthy adult men, and this anabolic action of IGF-I is more evident in nutritionally deprived individuals. The question of long term target tissue exposure to endogenously generated IGF-I bioavailability in response to restoration of DHEA levels was not addressed in the present experiment. Nevertheless, our findings represent the first demonstration of a biological effect of DHEA in men and women of advancing age. Further studies at selected target tissue responses are warranted.

Although we are fully cognizant of the limitations of self-reported mood-behavioral changes in response to an experimental agent, the self-reported increase in well-being by the large majority of our subjects during DHEA treatment should be viewed as a reliable outcome in this double blind, placebo-controlled study. Self-reported changes include increased energy, deeper sleep, improved mood, more relaxed feeling,

and better ability to handle stressful events. The lack of corresponding changes in libido support the validity of the positive event of improved physical and psychological capacity during DHEA, but not placebo, treatment.

The mechanism underlying the array of individual well-being enhancements in response to replacement doses of DHEA in both men and women is unclear. It is unrelated to the small increments in potent androgens, as this occurred only in women. The possibility of a central effect of DHEA should be considered. Substantial experimental evidence now exists showing that DHEA and DS bind to the γ -aminobutyric acid_A-receptor complex and function as an antagonist or negative modulator, resulting in activation of neuronal excitability *in vitro* (see Ref. 50 for review). Further, a memory-enhancing effect and inhibition of aggressive behavior have been demonstrated *in vivo* (50). DHEA and DS have been found in the human brain and may mediate a distinct allosteric mode of interaction with the γ -aminobutyric acid_A receptor, as in rodents (50). However, it is not known whether incremental changes in circulating DHEA can be delivered to brain target sites. Alternatively, the potential improvement of cellular well-being by trophic effects of IGF-I may manifest as improved capacity of physical and psychological performances. To clarify these postulates would require a multidisciplinary approach.

In conclusion, our results support the hypothesis that DHEA may indeed have a biological function in man, and that restoration of DHEA and DS levels in age-advanced men and women with a replacement dose of DHEA induced an increase in bioavailable IGF-I, which, with time, may result in an improvement in catabolic processes and physical/psychological well-being. Future trials are warranted to identify the biological end points of elevated bioavailable IGF-I in healthy aging individuals.

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